FEDERAL SECURITY AGENCY
PUBLIC HEALTH SERVICE

IN REPLYING, ADDRESS THE

Tuberculosis Research Laboratory,
411 East 69th St., New York 21, N. Y.

September 28, 1951.

Dr. Joshua Lederberg,
Department of Genetics,
The University of Wisconsin,
College of Agriculture,
Madison 6, Wisconsin.

Dear Joshua:

The replica plating method has been working beautifully. I am not sure it will be too useful, however, for isolating a POB mutant since this factor is heavily excreted by wild type. Reconstruction experiments on a mixture of wild type with a mutant requiring PABA, which is also excreted by wild type, showed that even at fairly low population densities (50-100 colonies per plate) the mutants grew on minimal as well as supplemented medium. They could be distinguished from wild type only by their smaller colony size at fairly early stages in cultivation. Since the lag period immediately after exposure to penicillin is highly variable, many mutant colonies appearing in our experience only after three days, it might be necessary to introduce intermediate cultivation between a penicillin exposure and replica plating.

I enjoyed reading your manuscript on this subject which Werner borrowed from Aaron. I recall that you had quite a complete bibliography on the evidence for spontaneous mutation to drug resistance, and wonder whether you got hold of the following reference, which I ran into last night: Yegian, Budd, and Vanderlinde, J. Bact. 58, 257 (1949).

We have a few results on the strains you sent. W1504 was a mixture of tyrosine and proline auxotrophs (I hope this disclosure won't discourage you from sending more!). PF-4 was a prototroph from which we couldn't recover any tryptophan auxotrophs. PF-11 requires a rather high concentration of Yeast Extract and does not respond to mixtures of any of the factors we have on hand; this would be nice to look into, but doesn't fit our plans at the moment. PF-21, in addition to its leucine requirement, responds to a mixture of arginine and a pyrimidine. This double requirement has been previously encountered by Roepke as quoted by Tatum in the Cold Spring Harbor Symposium, and we have also picked it up before. I am very grateful for it as I have been planning , with our strain, to look into the possibility that Philip Cohen's citrulline

precursor might be a growth factor for this strain. PF-3, phenylalanine auxotroph of Pseudomonas, is particularly interesting since it resembles our coli mutants in this group, and the Salmonella ones you sent, in responding to phenylpyruvic acid as well as phenylalanine, but it differs in not excreting any tyrosine.

Thanks for the information about dried silica jell. We nearly lost a couple of valuable strains over the summer and will certainly try this technique.

I gather you didn't care much for the papers of Zeller and Yegian in recent issues of the Journal of Bacteriology. I haven't got around to reading the first, but I don't have any strong reaction to the second. The facts reported in it are of great interest to me and I am delighted to be able to include them in the manuscript I have been preparing on the PNBA-sulfonamide story. Yegian's interpretation seems to me naive in that he doesn't consider any possibility other than the action of the two drugs on different enzymes, - but for a man who has been working on tubercle bacilli in a sanitorium for 20 years I hardly would expect anything better; in fact, considering his background I was really quite favorably impressed by his general analysis of the problem of drug resistance in tubercle bacilli in the American Review of Tuberculosis: Yegian, D., and R. J. Vanderlinde, Am. Rev. Tuberc. 61, 483 (1950). As I got the story from Gardiner Middlebrook, Yegian went to a tuberculosis sanitorium without any scientific training and is literally a self-made man in this field. I trust you will forgive me for this temporary excess of charity!

Sincerely yours,

Bernard D. Davis

BDD/hl

P.S. - Results on growth requirements of your multiple aromatics have just come through; we are planning to look into their accumulations next. In general, I would say you have under-estimated their requirements for rapid growth. We verify your labelling of W-1426 as a triple (Ty- φ-trypt). We find that SW-38 is a triple rather than double, W-1427 a mixture of triple and quadruple rather than tyrosine or tryptophan, W-1104 and W-1150 are quadruple rather than triple. You may not have picked up their PAB requirement unless your glassware, etc., is very clean, since the amount required is very small.

B.D.D.